

REVIEW

Mechanisms of ethanol-induced cardiac damage

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Although the extent of excessive ethanol consumption merits serious concern, and the association between such consumption and dilated cardiomyopathy is increasingly recognised, the pathogenesis and factors that determine patient susceptibility are still poorly known. Until the 1950s the cause of ethanol-induced cardiomyopathy was supposed to be nutritional deficiencies (that is, disturbances of nutrient handling or limitations in supply). Though dietary deficiencies (for example, thiamine) can cause cardiomyopathy, the distinction between alcoholic heart muscle disease (AHMD) and beriberi heart disease was demonstrated only when cardiac dysfunction was shown to occur in the absence of nutritional deficiencies and when AHMD failed to respond to thiamine.¹ Furthermore, the use of appropriate pair-feeding regimens using nutritionally complete liquid diets has also shown that experimental alcohol-induced cardiac abnormalities can occur without overt nutritional deficiencies.²

Alcohol heart muscle disease

The clinical diagnosis of alcohol heart muscle disease (AHMD) reflects the coexistence of global myocardial dysfunction in a heavy drinker in whom no other cause for myocardial disease has been found.³ We have shown that among patients with dilated cardiomyopathy there is a group characterised by a high alcohol intake and raised concentrations of myocardial tissue enzymes. This finding supports the concept of AHMD as a distinct entity.⁴ More recently, a direct correlation between alcohol consumption and abnormal left ventricular function has been shown,⁵ suggesting that ethanol exerts a dose-related toxic effect on cardiac muscle.

The risk of developing AHMD is related to both mean daily alcohol intake and duration of drinking,^{4,5} but there is much individual susceptibility to the toxic effect of alcohol. Women are peculiarly resistant to AHMD,⁶ and the reasons for this are unknown. In contrast, studies have clearly shown that women are more susceptible to the development of alcoholic liver disease.^{7,8} Individual sensitivity to alcohol may be related to various factors, including pre-existing cardiac disease, hypertension, cigarette smoking, immune influences, or genetic differences in alcohol metabolism etc.

Toxic effects of ethanol

The direct toxic effect of alcohol on the heart

has been established in both laboratory animals and in humans.^{2,9,10} For example, alterations in mitochondrial ultrastructure and dilatation of the sarcoplasmic reticulum have been shown after an acute infusion of alcohol in patients with heart disease.¹¹ These changes correlate with decreased mitochondrial function in animal models and include decreased respiratory rates with various substrates¹² and impaired fatty acid oxidation.¹³ Though the acute effects of alcohol on ventricular function, myocardial ultrastructure, and myocardial metabolism are well documented^{9,10} the relation of these changes to the pathogenesis of clinical cardiac disease, as manifest by cardiac failure and arrhythmias, is less clear. The more discrete changes in cardiac metabolism may be responsible for arrhythmias that occur in response to alcohol in the absence of obvious cardiomyopathy.¹⁴

Most patients in whom AHMD develops have been drinking over 80 g/day for over 10 years.⁴ Damage also seems to be more common with consistent heavy drinking rather than binge drinking. Certainly, the causal relation between increasing alcohol consumption and hypertension are well established as exemplified by the Framingham studies (reviewed by McCall⁹) and more recently by Bray and Edwards¹⁵ and Yamada *et al.*¹⁶ The effects of alcohol on the myocardium are thought to be reversible in the early stages: abstinence significantly increased the left ventricular ejection fraction and reduced the abnormal cardiothoracic ratio.¹⁷ The transition from reversible alcohol-induced injury to permanent organ damage is not understood.

Mechanism of ethanol-induced cardiac damage

The elucidation of the mechanisms involved in the pathogenesis of AHMD are complicated by the fact that ethanol is metabolised in the liver, mainly by alcohol dehydrogenase to acetaldehyde, which is further metabolised to acetate by acetaldehyde dehydrogenase.¹⁸ This implies that alcohol, acetaldehyde, or acetate may be the candidate metabolite responsible for AHMD. Though most research has been targeted on the myotoxicity of alcohol and acetaldehyde, acetate also alters cardiac function.¹⁹ However, investigations in this area are confounded by the fact that alcohol and acetaldehyde can induce additional organ damage—for example, of the liver, kidneys, and endocrine glands—which in turn can cause gross metabolic dis-

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turbances and ultimately affect the heart itself. This raises the question of whether ethanol or acetaldehyde induce cardiac abnormalities directly or indirectly. Evidence to support the direct toxic effects of alcohol has been obtained from studies of isolated tissue for example, those showing that both alcohol and acetaldehyde reduce the Na^+ , K^+ -activated ATPase activities of the myocardial plasma membranes.²⁰

Direct effects on cardiac electromechanical coupling by inhibition of calcium-myofilament interaction have also been shown in vitro.²¹ Acetaldehyde also covalently forms protein adducts in vitro, including those with actin.²² Indirect effects of alcohol may also include disturbances in immune function, which also occur in idiopathic dilated cardiomyopathy.²³ It is not known whether similar mechanisms occur in AHMD, but autoimmune mechanisms have been postulated in the development and progression of alcoholic liver disease.²⁴

Recent interest has concentrated on two main mechanisms:

FREE RADICAL DAMAGE

Free radicals are molecules or molecular fragments with unpaired electrons (reviewed by Slater²⁵) that are highly reactive with biological substances, such as membranes, DNA, and key metabolites. The metabolism of excessive amounts of alcohol induces the hepatic microsomal cytochrome P450IIE1 with an increased production of reactive oxygen species.^{18,26} These may deplete the antioxidant pool. Furthermore, the enhanced ethanol oxidation rates in regular heavy drinkers (>80 g/day) would be expected to increase production of these damaging species. Acute ethanol consumption also induces tissue damage mediated by free radicals.^{27,28} It has been suggested that reactive oxygen species, including the extremely reactive hydroxyl radical, exert their cytotoxic effects by causing peroxidation of membrane phospholipids, which increases membrane permeability and impairs membrane function.²⁵ Free radicals have been shown to be toxic to the myocardium.^{29,30} They have also been reported to affect excitation-coupling.³¹ Also, hydroxyl radicals induce striking

alterations in the Ca^{2+} -activated ATPase activity of cardiac myofibrils.³² The highly reactive nature of hydroxyl radicals accords with the observation that their acute generation alters the electrophoretic pattern of cardiac myofibrillar proteins, in particular those of the myosin heavy chain—probably by polymerisation.³² These effects may induce or contribute to myocardial damage in AHMD. Increased concentrations of conjugated dienes have been shown in the serum³³ and liver³⁴ of chronic heavy drinkers, further suggesting free radical-induced damage by alcohol. However, lipid peroxidation products may be a consequence rather than a cause of hepatic damage.³⁵

Studies in chronic heavy drinkers suggested that plasma antioxidant status is a major determinant of skeletal muscle myopathy.³⁶ The plasma antioxidant status of patients with alcoholic myopathy is significantly lower than that of alcoholics with normal muscle histology. Paradoxically, we found no evidence that plasma antioxidant status in patients with AHMD was lower than in patients with dilated cardiomyopathy.³⁷ Similarly, there was no evidence of reduced plasma antioxidant status in patients with AHMD who showed type II fibre atrophy on skeletal muscle biopsy compared with those with normal histology.³⁷ These results indicate that there are ample supplies of antioxidants within the plasma to combat reactive oxygen species in patients with AHMD. It is, however, uncertain whether plasma antioxidant concentrations reflect cardiac status and this indicates that cardiac antioxidant status should be directly assessed: the application of diagnostic biopsy procedures will be helpful.

DEFECTS IN PROTEIN SYNTHESIS

Many experimental studies of the relation between cardiac protein synthesis and ethanol toxicity have been directed towards in vitro systems.³⁸ Though these techniques are often useful for dissecting out biochemical events, eventually the data from isolated cells or organs have to be applicable to intact animals or humans. Various methods have been developed for investigating cardiac protein metabolism in vivo and the "flooding dose" technique of Garlick *et al*³⁹ is perhaps the

Table 1 Effect of acute ethanol dosage on cardiac protein synthesis in vivo

Treatment	Protein fraction	Fractional synthesis rate of myocardial protein (% control)	p
Control	Mixed	100	
	Myofibrillary	100	
Ethanol	Mixed	79	<0.01
	Myofibrillary	78	<0.01
	Mitochondria, sub-sarcolemmal	77	<0.01
	Mitochondria, interfibrillar	74	<0.05
Acetaldehyde	Mixed	87	NS
	Myofibrillary	95	NS
Ethanol plus 4-methylpyrazole	Mixed	79	<0.01
	Myofibrillary	81	<0.01
Ethanol plus cyanamide	Mixed	20	<0.001
	Myofibrillary	20	<0.001

All ethanol dosage studies entailed intraperitoneal administration at 75 mmol/kg body weight. Protein synthesis was measured in vivo by the method of Garlick *et al*³⁹ after 2.5 h. Acetaldehyde, which is volatile and toxic, could only be injected at a dosage of approx 3 mmol/kg body weight. Protein synthesis was also measured after 2.5 h. Controls were injected with an equal volume of saline (0.15 mol/l sodium chloride). The data came from various unpublished studies (Siddiqi T, Richardson P J, Preedy V R).

Table 2 Protein synthesis in experimental chronic established left ventricular hypertrophy in response to acute ethanol toxicity

Treatment	Fractional synthesis rate of myocardial protein (% control)	p
Mixed:		
Control	100	
Hypertrophy	85	NS
Control + ethanol	80	< 0.05
Hypertrophy + ethanol	61	< 0.01
Myofibrillary:		
Control	100	
Hypertrophy	80	< 0.05
Control + ethanol	78	< 0.05
Hypertrophy + ethanol	61	< 0.01
Cytoplasmic:		
Control	100	
Hypertrophy	94	NS
Control + ethanol	71	< 0.05
Hypertrophy + ethanol	48	< 0.01

Cardiomyopathic changes were induced in the left ventricle of rats by chronic hypertension (30 days). The rats were injected intraperitoneally with ethanol (75 mmol/kg body weight). Protein synthesis was measured in vivo 2.5 h after ethanol administration. See footnote to table 1.

most useful and accurate method currently available. It superseded procedures that had previously presented problems when tracer amounts of labelled amino acids were given, for example by the "constant infusion" technique.⁴⁰ The flooding dose method has been used to study cardiac protein metabolism in the laboratory rat.^{41,42} To study the toxic effects of ethanol on cardiac protein synthesis in vivo we have also used the flooding dose method devised for labelled phenylalanine. We found that acute ethanol dosage reduced the fractional synthesis rate of cardiac mixed⁴³ and myofibrillary proteins (table 1), as well as of non-contractile protein (for example, soluble proteins (table 2)). Though the acute changes in protein synthesis were more modest (about 20%) than the effects on skeletal muscle, they were larger than in the liver (table 3). The effects of ethanol and associated metabolites on cardiac protein synthesis nevertheless may be of profound physiological and biochemical significance. These results again raise the important question whether the metabolites of ethanol metabolism—acetaldehyde or acetate—induce these effects.

We have attempted to answer some of these fundamental questions by the in vivo use of appropriate inhibitors of ethanol metabolism such as 4-methylpyrazole and cyanamide, which inhibit alcohol dehydrogenase and acetaldehyde dehydrogenase, respectively. This approach was used with some success in studies on liver and skeletal muscle and we used the same techniques to study experimental alcohol-induced heart disease. These results show that raising ethanol-derived acetaldehyde concentrations

considerably reduced cardiac protein synthesis (table 1). Protein synthesis also fell when acetaldehyde formation was inhibited. Our findings suggest that both alcohol and acetaldehyde reduce cardiac protein synthesis in vivo. In normal rats synthesis of both myofibrillary and non-myofibrillary proteins was equally affected (table 1). Various studies showed that acute ethanol toxicity considerably disturbs mitochondrial structure and function. Similarly, we found that the synthesis of mitochondrial proteins was inhibited by ethanol in vivo (table 1). Defects in ventricular myofibrillary protein turnover also occurred in chronic alcohol feeding. But, paradoxically, protein synthesis increases.⁴⁴ The nature of the adaptive mechanisms is unknown.

Table 2 shows that the reductions in left ventricular protein synthesis (about 15–20%) in rats with established chronic hypertension were slightly smaller than those caused by ethanol alone (about 20–30%). However, when ethanol was administered to rats with hypertrophied ventricles, protein synthesis in the contractile (myofibrillar) and non-contractile (cytoplasmic) fractions was considerably reduced. The most sensitive constituents occur in the cytoplasmic fractions, which includes soluble proteins such as the enzymes responsible for metabolic functions, where protein synthesis in ethanol-exposed hypertrophied ventricles falls by half (table 2).

CONCLUDING REMARKS

Alcohol-induced cardiac damage and dysfunction are a relatively widespread phenomena that affect up to one third of those who misuse alcohol. In the United Kingdom

Table 3 Protein synthesis in different tissues in response to acute ethanol toxicity

Tissue	Mean fractional rate of protein synthesis (%/day)		Change (% control)	p
	Control	Ethanol		
Heart	18	14	-22	< 0.001
Gastrocnemius muscle	15	10	-30	< 0.001
Diaphragm	20	17	-15	NS
Bone	63	45	-29	< 0.001
Liver	86	78	-10	NS

Rats were acutely injected with ethanol (75 mmol/kg body weight, intraperitoneally) and fractional rates of protein synthesis (defined as the percentage of tissue protein renewed each day, that is, %/day) were measured in vivo 2.5 h after ethanol administration. See footnote to table 1.

about 1.5 million people drink too much alcohol, as do up to 10% of adults in Europe and North America. Excessive consumption of alcohol by teenagers and adolescents is causing increasing concern.

Excessive alcohol consumption can cause acute myocardial or cardiovascular disturbances, such as changes in blood pressure and arrhythmias and alcoholic heart muscle disease. The mechanisms responsible for these alterations are inadequately understood, but likely candidates have been reviewed. It could be argued that as the causative agent is known the cure is self-evident. However, the American experience of prohibition showed that strategies for curbing consumption of alcohol are not reliable. Also there is evidence for a genetic basis for alcoholism and related problems.^{45,46} Detailed studies of the pathogenesis of alcoholic myocardial disease may help us to understand how other toxin-induced cardiac abnormalities occur.

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